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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re application of:

Avi ASHKENAZI, et al.

Application Serial No. 09/903,640

Filed: July 11, 2001

For: **SECRETED AND TRANSMEMBRANE  
POLYPEPTIDES AND NUCLEIC  
ACIDS ENCODING THE SAME**

) Examiner: Ketter, James

) Art Unit: 1636

) Confirmation No. 3104

) Attorney's Docket No. 39780-1618 P2C48

) Customer No. 35489

EXPRESS MAIL LABEL NO. EY 765 978 214 US

DATE MAILED: AUGUST 15, 2006

**PRELIMINARY RESPONSE**

**MAIL STOP: RCE**

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Dear Sir:

In the above identified application, a Final Office Action was mailed on February 22, 2006 and a response was timely filed before the two month date on April 20, 2006, with a Declaration by Dr. Paul Polakis (with attached Exhibits A and B). No Advisory Action was mailed. A Notice of Appeal was filed on May 22, 2006 with required fees.

This Preliminary Response accompanies a Request for Continued Examination (RCE) under 37 CFR §1.114 for the above identified application, and is filed with a petition for a one-month extension of time with necessary fees.

This submission is accompanied by a Declaration under 37 C.F.R. §1.132 by Dr. Randy Scott and with an Information Disclosure Statement, with copies of additional references in support of the Applicants' arguments. Applicants respectfully request that the previous response, the Polakis Declaration, the Information Disclosure Statement and the Scott Declaration be made of record in the above-identified application, and be considered by the Examiner.

**Pending Claims** are reflected in the listing of claims that begins on page 2 of this paper.

**Remarks/Arguments** begin on page 3 of this paper.

**Pending Claims:**

- 1-43. (canceled)
44. (previously presented) An isolated polypeptide comprising:
- (a) the amino acid sequence of the polypeptide of SEQ ID NO: 263;
  - (b) the amino acid sequence of the polypeptide of SEQ ID NO: 263, lacking its associated signal peptide;
  - (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 263; or
  - (d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209481;
- wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon tumors.
45. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 263.
46. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 263, lacking its associated signal peptide.
47. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 263.
48. (canceled)
49. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209481.
50. (previously presented) A chimeric polypeptide comprising a polypeptide according to Claim 44 fused to a heterologous polypeptide.
51. (previously presented) The chimeric polypeptide of Claim 50, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.



DECLARATION OF RANDY SCOTT, Ph.D. UNDER 37 C.F.R. § 1.132

I, Randy Scott, Ph.D. declare and say as follows:

1. I hold a Bachelor of Science degree in Chemistry from Emporia State University and a Ph.D. in Biochemistry from the University of Kansas.
2. I am Chairman and Chief Executive Officer of Genomic Health, Inc., a life science company founded in August of 2000 located in Redwood City, California, conducting sophisticated genomic research to develop clinically validated molecular diagnostics, which provide individualized information on the likelihood of disease recurrence and response to certain types of therapy.
3. In 1991, I co-founded Incyte Pharmaceuticals, Inc., the world's first genomic information business. I served the company in multiple capacities, including Chairman of the Board from August 2000 to December 2001, President from January 1997 to August 2000, and Chief Scientific Officer from March 1995 to August 2000. Under my leadership, Incyte has created the LifeSeq Gold® gene sequence and expression database, an industry standard and the most comprehensive collection of biological information in the world. I have also led Incyte to expand its focus beyond gene sequence databases to include the research and application of gene expression, SNPs (single nucleotide polymorphisms), and proteomics.
4. I am an inventor on several issued patents, and authored over 40 scientific publications in the fields of protein biology, gene discovery, and cancer.
5. My Curriculum Vitae is attached to and serves part of this Declaration.
6. All statements made in this Declaration are based on my more than 15 years of personal experience with the DNA microarray technique and its various uses in the diagnostic and therapeutic fields, and my familiarity with the relevant art.
7. The DNA microarray technology is based on hybridizing arrayed nucleic acid probes of known identity with target nucleic acid to determine the identity and/or expression levels (abundance) of target genes. DNA microarrays work by exploiting the ability of a given

mRNA molecule to hybridize to the DNA template from which it originated. By using an array containing many DNA samples, scientists can determine, in a single experiment, the expression levels of hundreds or thousands of genes within a sample by measuring the amount of mRNA bound to each site on the array. The amount of mRNA bound to the spots on the microarray is precisely measured, generating a profile of gene expression in the sample.

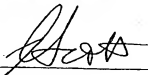
8. DNA microarray analysis has been extensively used in drug development and in diagnosis of various diseases. For instance, if a certain gene is over-expressed in a particular form of cancer relative to normal tissue, researchers use microarray chips to determine whether a drug candidate will reduce over-expression, and thereby cause cancer remission. In addition, if a gene has been identified to be over-expressed in a certain disease, such as a certain type of cancer, it can be used to diagnose that disease. Due to its importance in drug discovery and in the field of diagnostics, microarray technology has not only become a laboratory mainstay but also created a world-wide market of over \$600 million in the year of 2005. A long line of companies, including Incyte, Affymetix, Agilent, Applied Biosystems, and Amersham Biosciences, made microarray technology a core of their business.

9. Correlation between mRNA and protein levels can be assessed by a variety of methods suitable for measuring protein expression levels, including, for example, SDS-polyacrylamide gel electrophoresis (SDS-PAGE), two-dimensional fluorescence-difference gel electrophoresis (DIGE), mass spectrometric approaches, microsequencing, and a combination of these and similar known techniques, however, direct measurement of protein expression levels remains non-trivial.

10. One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the Patent.

Date: August 11, 2006

  
Randy Scott, Ph.D.

SV 2202107 v1  
8/11/06 11:00 AM (39766.7000)

Randy W. Scott, Ph.D.  
Genomic Health  
301 Penobscot  
Redwood City, CA 94022

**EDUCATION:**

1979 B.S., Chemistry, Emporia State University, Emporia Kansas  
1983 Ph.D., Biochemistry, University of Kansas, Lawrence Kansas

**WORK EXPERIENCE:**

- 2000-present **GENOMIC HEALTH, INC.,** Cofounder
- Chairman & CEO (2000-present)  
Founded a new genomics company and raised over \$100 million to bring personalized medicine to clinical practice. Selected by Red Herring Magazine as one of the Top 100 private technology companies in North America in 2005
- 1991-2000 **INCYTE, Cofounder**
- Chairman of the Board (2000-2001)  
Helped lead the transition to a new management team and transition to drug development
  - President and Chief Scientific Officer (1997-2000)  
Responsible for Research & Development, Operations, Marketing & Sales. Built the world's first genomic information business with peak sales of over \$200 million per year including 19 out of the world's top 20 pharmaceutical companies as subscribers
  - Vice President and Chief Scientific Officer (1991-1997)  
Built recombinant DNA therapeutic product portfolio and led the launch of the genomics business
- 1985-91 **INVITRON CORPORATION**
- Sr. Director of Research (1998-1991)  
Responsible for Research & Development.
  - Director of Protein Biochemistry (1985-1988)  
Responsible for building the protein purification group for a cGMP manufacturing facility producing recombinant proteins, including monoclonal antibodies, tPA and Factor VIII.
- 1983-85 **UNIGENE LABORATORIES, Fairfield, New Jersey**
- Sr. Scientist, Dept. of Protein Biochemistry  
Led effort to work on IgA proteases linked to meningococcal infections

**OTHER EXPERIENCE:**

- 2005- Present **AMERICAN CLINICAL LABORATORY ASSOCIATION**
- Member, Board of Directors
- 1997-2000 **DIADEXUS, INC., Cofounder**
- Member, Board of Directors (1997-2000)  
Worked with George Poste (CSO, SmithKline, Beecham) to establish a diagnostics joint venture between Incyte and SmithKline

**Awards:**

2001 Genome Technology Magazine 2001 All-Star  
1999 Forbes Magazine list of Biotech's Top 25 Influential Insiders

- 1997 Ernst & Young/NASDAQ Silicon Valley Entrepreneur of the Year for Life Sciences
- 1987 Small Business Innovation Research Grant Award (Principal Investigator): "Azurophil-Derived Bactericidal Factor" Grant # SSS-5 (K) 1R43A124409-011987
- 1983 Phillip Newmark Research Award, University of Kansas, 1983
- 1982 Borgendale Graduate Seminar Award, University of Kansas.

#### Publications:

- Low, D.A., Cunningham, D.D., Scott, R.W., and Baker, J.B., "Interactions of Serine Proteases with Human Fibroblasts: Regulation by Protease Nexin, A Cellular Component with Similarities to Antithrombin III." in Receptor-Mediated Binding and Internalization of Toxins and Hormones (Middlebrook, J.L. and Kohn, L.S. eds.) pp. 259-270, Academic Press, New York (1982).
- Low, D.A., Scott, R.W., Baker J.B., and Cunningham, D.D., Cells Regulate their Mitogenic Response to Thrombin through Release of Protease Nexin. Nature 298, 476-478 (1982).
- Scott, R.W., "Purification, Characterization, and Functional Studies of Protease Nexin." Ph.D. Thesis, University of Kansas (1983).
- Scott, R.W., Eaton, D.L., Duran, N. and Baker, J.B. Regulation of Extracellular Plasminogen Activator by Human Fibroblasts. The Role of Protease Nexin. J. Biol. Chem. 258, 4397-4403 (1983).
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- Scott, R.W., Bergman, B., Bajpai, A., Hersh, R., Rodriguez, H., Jones, B.N., Barreda, C., Watts, S., and Baker, J.B. Protease Nexin: Properties and a Modified Purification Procedure. J. Biol. Chem. 7029-7034 (1985).
- Bergman, B.L., Scott, R.W., Bajpai, A., Watts, S., and Baker, J.B., Inhibition of Tumor-Cell Extracellular Matrix Destruction by a Fibroblast Proteinase Inhibitor, Protease Nexin I. Proc. Nat. Acad. Sci. 83, 996-1000 (1986).
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- Scott, R.W., Duffy, S.A., Moellering, B.J., and Prior, C., Purification of Monoclonal Antibodies from Large-Scale Mammalian Cell Culture Perfusion Systems. Biotechnology Progress 3, 49-56 (1987).
- Baker, J.B., McGrogan, M., Simonsen, C.C., Scott, R.W., Gronke, R.S. and Honeyman, A., "Protease Nexin I. Structure and Potential Functions." In The Pharmacology and Toxicology of Proteins, Winkelhake, J.L., Holcenberg, J.S., eds., Alan R. Liss, Inc., New York, (1987).
- Scott R.W., "Large-scale Production of Biopharmaceuticals from Mammalian Cells" in Clinical Applications of Genetic Engineering (Larry C. Lasky and JoAnn Edwards-Moulds eds.) American Association of Blood Banks, Arlington, Virginia (1987).
- McGrogan, M., Kennedy, J., Li, M.P., Hsu, C., Scott, R.W., Simonsen, C.C., and Baker, J.B., Molecular Cloning and Expression of Two Forms of Human Protease Nexin I, BioTechnology 6: 172 (1988).
- Otsuka FL, Cance WG, Dilley WG, Scott RW, Davie JM, Welch MJ, Wells SA Jr., A Potential New Radiopharmaceutical for Parathyroid Imaging: Radiolabeled Parathyroid-specific Monoclonal Antibody -I.



Evaluation of 125-I-labeled Antibody in a Nude Mouse Model System. *Int. J. Rad. Appl. Instrum. B.* 15:305-11, 1988

Otsuka FL, Cance WG, Dilley WG, Scott RW, Davie JM, Wells SA Jr., Welch MJ. A Potential New Radiopharmaceutical for Parathyroid Imaging: Radiolabeled Parathyroid-specific Monoclonal Antibody - II. Comparison of 125-I and 111-In-labeled Antibodies. *Int. J. Rad. Appl. Instrum. B.* 15:305-11, 1988

Prior, C.P., Doyle, K.R., Duffy, S.A., Hope, J.A., Moellering, B.J., Prior, G.M., Scott, R.W. and Tolbert, W.R. The Recovery of Highly Purified Biopharmaceuticals from Perfusion Cell Culture Bioreactors. *J. Parenteral Science and Technology* 43: 15-23 (1989).

McGrogan, M., Simonsen, C., Scott, R., Griffith, J., Ellis, N., Kennedy, J., Campanelli, D., Nathan, C., and Gabay, J., Isolation of a Complementary DNA Clone Encoding a Precursor to Human Eosinophil Major Basic Protein. *J. Exp. Med.* 168: 2295-2308 (1988).

Wilde, C.G., Griffith, J.E., Marra, M.N., Snable, J.L. and Scott R.W., Purification and Characterization of Human Neutrophil Peptide 4, a Novel Member of the Defensin Family, *J. Biol. Chem.* 264: 11200-11203 (1989).

Gabay, J.E., Scott, R.W., Campanelli, D., Griffith, J., Wilde, C., Marra, M.N., Seeger, M., and Nathan, C.F., Antibiotic Proteins of Human Polymorphonuclear Leukocytes, *Proc. Natl. Acad. Sci.* 86: 5610-5614 (1989).

Marra, M.N., Wilde, C.G., Griffith, J.E., Snable, J.L., and Scott R.W., Bactericidal/Permeability-Increasing Protein has Endotoxin Neutralizing Activity, *J. Immunol.* 144, 662-666 (1990)

Wilde, C.G., Snable, J.L., Griffith, J.E., and Scott R.W. Characterization of Two Azurophil Granule Proteases with Active Site Homology to Neutrophil Elastase, *J. Biol. Chem.* 265: 2038-2041 (1990).

Moellering, B.J., Tedesco, J.L., Scott, R.W., Towensend, R.R., Hardy, M.R., and Prior C.P. Molecular Differences Observed in a Monoclonal Antibody Expressed in Ascites Fluid, Serum-containing and Serum-free Cell Culture Conditions. *Biopharm.* pp. 30-38 February (1990).

McGrogan, M., Kennedy, J., Golini, F., Ashton, N., Dunn, F., Bell, K., Tate, E., Scott, R.W., and Simonsen, C.C., "Structure of the Human Protease Nexin Gene and Expression of Recombinant forms of PN-1." in *Serine Proteases and Serpins in the Nervous System* (B.W. Festoff ed.) pp.147-161 Plenum Press New York (1990).

Percira, H.A., Spitznagel, J.K., Winton, E.F., Shafer, W.M., Martin, L.E., Guzman, G.S. Pohl, J., Scott, R.W., and Kinkade, J.M. Jr. The Ontogeny of a 57KD Cationic Antimicrobial Protein of Human Polymorphonuclear Leukocytes: Localization to a Novel Granule Population. *Blood* 76:825-834, 1990.

Evans DL, McGrogan M, Scott RW, Carrell RW, Protease Specificity and Heparin Binding and Activation of Recombinant Protease Nexin I, *J. Biol. Chem.* 266:22307-12, 1991

Marra, M.N, C.G. Wilde, M.S. Collins, J.L. Snable, M.B. Thornton, and R.W. Scott, The Role of Bactericidal/Permeability-Increasing Protein as a Natural Inhibitor of Bacterial Endotoxin. *J. of Immunol.* 148:532-537, 1992.

Scott R. W., Wilde C.G., Lane J.C., Snable, J.L., and Marra M.N., "Antimicrobial and Antidotoxin Activities of Bactericidal/Permeability-Increasing Protein In Vitro and In Vivo" in *Bacterial Endotoxin: Recognition and Effector Mechanisms* (J. Levin, C.R. Alving, R.S. Munford, and P.L. Stutz eds.) pp. 373-377 Elsevier Science Publishers B.V. (1993)

Stevens, P., Scott R.W., Shatzen E.M., Recombinant Human Protease Nexin-1 Prevents Articular Cartilage Degradation in the Rabbit *Agents and Actions Suppl* 39:173-7 in press 1993

Marra M.N., Thornton M.B., Snable J.L., Leong S., Lane J., Wilde C.G., and Scott R. W., Regulation of the Response to Bacterial Lipopolysaccharide by Endogenous and Exogenous Lipopolysaccharide Binding Proteins" *Blood Purif.* 11:134-140, 1993

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Marra M.N., Thornton M.B., Snable J.L., Wilde C.G., Scott R.W., Endotoxin-binding and -neutralizing Properties of Recombinant Bactericidal/Permeability-Increasing Protein and Monoclonal Antibodies HA-1A and E5 *Critical Care Medicine* 22:559-65, 1994

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Scott RW, Gene Patents and Other Genomic Inventions. Published Hearing before the Subcommittee on Courts and Intellectual Property of the Committee on the Judiciary House of Representatives, One Hundred Sixth Congress, Second Session, July 13, 2000 Serial No. 121. pp. 44-55. U.S. Government Printing Office Washington, 2000

#### Issued Patents:

U.S. Patent # 4,898,826 Issued Feb. 6, 1990  
A Method for Solubilization of Tissue-Type Plasminogen Activator.

U.S. Patent # 5,006,252 Issued April 9, 1991  
Recombinant Purified Protease Nexin.

U.S. Patent #5,032,574 Issued July 16, 1991  
Novel Antimicrobial Peptide, Compositions Containing Same and Uses Thereof.

U.S. Patent #5,087,368 Issued Feb. 11, 1992  
Purified Protease Nexin

U.S. Patent #5,089,274 Issued Feb. 18, 1992

Use of Bactericidal/Permeability Increasing Protein or Biologically Active Analogs Thereof to Treat Endotoxin-Related Disorders

U.S. Patent #5,112,608 Issued May 12, 1992

Use of Protease Nexin-1 to Mediate Wound Healing

U.S. Patent #5,171,739 Issued December 15, 1992

Treatment of Endotoxin-Associated Shock and Prevention Thereof Using a BPI Protein

U.S. Patent #5,187,089 Issued Feb. 16, 1993

Protease Nexin-1 Variants Which Inhibit Elastase

U.S. Patent #5,196,196 Issued March 23, 1993

Use of Protease Nexin-1 in Wound Dressings

U.S. Patent #5,206,017 Issued Apr. 27, 1993

Use of Protease Nexin-1 as an Anti-inflammatory

U.S. Patent #5,210,027 Issued May 11, 1993

DNA Encoding Novel Antimicrobial Polypeptide and Methods for Obtaining Such Polypeptide

U.S. Patent #5,278,049 Issued January 11, 1994

Recombinant Molecule encoding Human Protease Nexin

U.S. Patent #5,234,912 Issued August 10, 1993

Pharmaceutical Compositions Comprising Recombinant BPI Proteins and a Lipid Carrier and Uses Thereof

U.S. Patent #5,278,049 Issued January 11, 1994

Recombinant Molecule encoding Human Protease Nexin

U.S. Patent #5,308,834 Issued May 3, 1994

Treatment of Endotoxin-Associated Shock and Prevention Thereof Using BPI Protein

U.S. Patent #5,326,562 Issued July 5, 1994

Pharmaceutical Dosage Unit for Treating Inflammation Comprising Protease Nexin-1

U.S. Patent #5,234,912 Issued August 10, 1993

Pharmaceutical Compositions Comprising Recombinant BPI Proteins and a Lipid Carrier and Uses

U.S. Patent #5,278,049 Issued January 11, 1994

Recombinant Molecule Encoding Human Protease Nexin

U.S. Patent #5,326,562 Issued July 5, 1994

Pharmaceutical Dosage Unit for Treating Inflammation Comprising Protease Nexin-1

U.S. Patent #5,334,584 Issued August 2, 1994

Recombinant, Non-Glycosylated BPI Protein and Uses Thereof

U.S. Patent #5,457,090 Issued October 10, 1995

Protease Nexin-1 Variants

U.S. Patent #5,470,825 Issued November 28, 1995

Basophil Granule Proteins

U.S. Patent #5,476,839 Issued December 19, 1995

Basophil Granule Proteins

U.S. Patent #5,495,001 Issued February 27, 1996  
Recombinant Purified Protease Nexin

U.S. Patent #5,747,283 Issued May 5, 1998  
Basophil Granule Proteins

U.S. Patent #5,770,694 Issued June 23, 1998  
Genetically Engineered BPI Variant Proteins

U.S. Patent #5,840,484 Issued November 24, 1998  
Comparative Gene Transcript Analysis

U.S. Patent #6,114,114 Issued September 5, 2000  
Comparative Gene Transcript Analysis

U.S. Patent #6,093,801 Issued July 25, 2000  
Recombinant Analogs of Bactericidal/Permeability Increasing Protein

U.S. Patent #6,160,104 Issued December 12, 2000  
Markers for Peroxisomal Proliferators

U.S. Patent #6,160,105 Issued December 12, 2000  
Monitoring Toxicological Responses

U.S. Patent #6,265,187 Issued July 24, 2001  
Recombinant Endotoxin Neutralizing Proteins

U.S. Patent #6,403,778 Issued June 11, 2002  
Toxicological Response Markers

U.S. Patent #6,372,431 Issued April 16, 2002  
Mammalian Toxicological Response Markers

U.S. Patent #6,553,317 Issued April 22, 2003  
Relational database and system for storing information relating to biomolecular sequences and reagents